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THE ALLERGIC ORIGIN OF ZIRCONIUM DEODORANT GRANULOMAS.*

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LAST year, American dermatologists witnessed with considerable interest the appearance of a nova in the dermatological heavens. They saw a unique and highly distinctive clinical entity. First sighted by Weber and his group in Chicago, it has since been recognized and studied by clinicians and dermatopathologists from coast to coast. In this paper, we record our clinical and experimental studies on the nature and cause of this new dermatosis.

The first published reports by Weber and collaborators (Weber *et al.*, 1956 ; Rubin *et al.*, 1956 ; Weber and Neuhauser, 1957 ; Rubin, 1957) were followed by a number of society case presentations and recently by a report by Sheard and his group (Sheard *et al.*, 1957). In all, there are 64 reported cases. To this we may add 6 cases described herein. From a study of these 70 cases, it is possible to secure a well integrated over-all picture of the clinical characteristics of this disorder.

Although variously entitled "granuloma of the axillae caused by deodorants", "granulomatous reaction to deodorant sticks", "axillary granuloma", "sarcoid-like eruption of the axillae" and "zirconium granuloma", the disease pattern is strikingly uniform and diagnostic. It is invariably found in the axillae and appears as a chronic papular eruption (Fig. 1) which shows histologically a granulomatous pattern (Fig. 2, A and B). The key change is in the dermis. Epidermal changes

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are usually absent. Pruritus and acute inflammation are occasionally present. Predominantly seen in women, it has been reported in association with the use of deodorants and often with the practice of axillary shaving. No particular deodorant preparation was used exclusively by all affected, but the majority used a new stick deodorant containing sodium zirconium lactate. This so-called zirconium stick

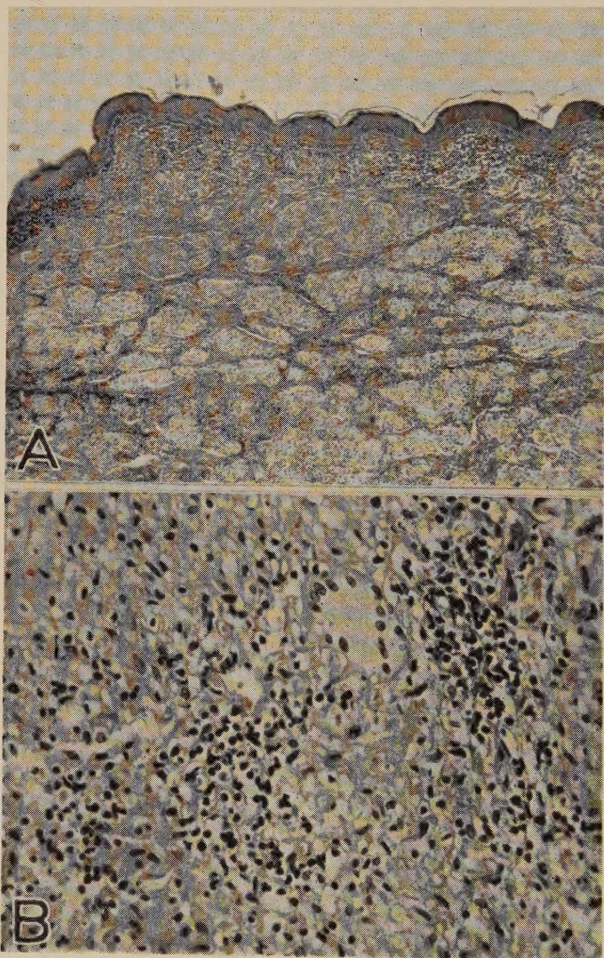


FIG. 2.—Histology of deodorant granuloma. Biopsy nine months after onset. Note nests of epithelioid cells, similar to sarcoid. Epithelioid cells in a typical granulomatous pattern. Note giant cell (top centre).

might have been used once only before the eruption or daily for months before any skin eruption was noted. It has regularly proven chronic, persisting for months or years. The numerous therapies which have been used include topical steroids, "dry ice", Grenz-rays, and X-rays. None of these has provided striking benefit and in most cases there has been very gradual spontaneous involution.

The cause of this new axillary granuloma has occasioned no less discussion than its treatment. The following lists the causes which have been considered in the literature.



FIG. 1.—Clinical appearance of zirconium deodorant granuloma. The eruption had been present three months. Histological appearances are shown in Fig. 2.

(i) Primary foreign-body reaction to :

Zirconium (Weber *et al.*, 1956 ; Sheard *et al.*, 1957 ; Rostenberg, 1957 ; Feldman, 1957).

Beryllium (Nelson, 1957).

Hafnium (Kalish, 1957).

Wax or lipid in stick vehicle (Zimmerman, 1957 ; Becker, 1957).

Other ingredients in vehicle (Michelson, 1957).

(ii) Secondary reaction to :

Apocrine sweat extravasation (Saunders, 1957*a, b* ; Price, 1957).

Follicular wall degeneration (Counter and Winer, 1957).

The possibility of an allergic or immune mechanism has also been mentioned (Pinkus and Botvinick, 1957 ; Hyman, 1957).

The results of our studies are presented under three major headings—literary, experimental and clinical.

LITERARY INVESTIGATION.

Two distinctive features characterize the new clinical entity : first, it is a granuloma and second, it is usually associated with the use of zirconium stick deodorants. These features led us to a review of the nature and cause of granulomas (with special reference to the skin) and to a study of the nature and granulomagenic potentiality of each of the chemicals found in zirconium stick deodorants.

(i) The Nature and Origin of Granulomas with special Reference to the Skin.

It is important to recognize that the term “granuloma” refers not to any clinical entity, but to a type of reaction-pattern of the skin or other tissue which is revealed solely by histological study.

A granuloma is a chronic local cellular reaction of diverse origin persisting for weeks in contrast to the acute inflammatory changes of a few hours or days. The distinctive cell of the granuloma is the so-called “epithelioid cell”. The term “epithelioid” is an old one based on the fact that although the cell is not derived from epithelium (e.g., epidermis), it has a vague morphological resemblance to the epithelial lineage of cells. This epithelioid cell which figures so prominently in the present problem is a faintly-staining, poorly-outlined cell which photographs indistinctly. It has an elongated vesicular nucleus. Irregular protoplasmic extensions of the cell may be seen, but generally the cells are so close-packed that the edges are not obvious.

What is the source and significance of this epithelioid cell? It is not seen in normal skin, but is derived from the macrophages or phagocytes of the body. These phagocytic cells are the scavenger cells which ingest debris and microscopic foreign material of all types. They pick up, for example, fragments of effete red blood cells, dying polymorphonuclear cells, tattoo pigment and bacterial residue. They originate in the reticulo-endothelial system and are of two sources, the monocytes of the blood and the histiocytes of connective tissue (in our case, dermis). Both cells have identical functions and some authorities believe them to be the same cell.

In chronic inflammation, local histiocytes are assisted by monocytes arriving in great numbers from capillaries in the affected site. Both cells attack foreign material and become indistinguishable so that the general term “macrophage” is best used to describe them. If foreign material remains visible in the cell, as in the case of a tattoo,

the term "macrophage" continues to be used to describe it. With fat ingestion, foamy cytoplasm develops, leading to the designation "foam cell". If the material cannot be visualized in the cell, the monocyte and histiocyte over a period of several weeks take on the appearance and name of "epithelioid cell".

Thus, the epithelioid cell is the mature, late stage of the functioning macrophage. It has a very long life, at times extending over years. This is in marked contrast to the polymorphonuclear *microphage* cell which survives for less than a week.

The patterns of aggregates of epithelioid cells and the presence of visible foreign material may permit the histopathologist to make diagnostic decisions, but at times epithelioid-cell reactions are none too distinctive. One aid is the appearance of epithelioid giant cells, which are very large cells resulting either from fusion or amitotic division of epithelioid cells. The Langhans-type giant cell has an arciform arrangement of nuclei and is seen in tuberculosis. The classical foreign-body-type giant cell has nuclei clumped in an irregular manner. This type is seen, for example, in paraffinomas of the skin.

Another diagnostic clue is the presence of absence or plasma cells, eosinophils and especially lymphocytes in the vicinity. A rim of lymphocytes about a tubercle of epithelioid cells is suggestive of tuberculosis, whereas its absence is a sarcoid pattern. In addition, the presence or absence of necrosis in the epithelioid-cell tubercle is of considerable help in the interpretation of possible causes.

Special examinations are of value in certain cases. All sections should be viewed with polarized light. Silica, cholesterol, certain lipids, starch and foreign particles such as hair or cotton fibres will show up, being doubly refractile. Unfortunately, zirconium cannot be visualized with this technique. Chemical analysis, spectroscopic studies and microincineration may be of help in specific instances. Finally, histochemical stains for iron, fat, calcium, and other compounds may be of value.

After a period of months or years, aggregates of epithelioid cells (granulomas) may show involution, with hyalinization and fibrosis. Some granulomas disappear without trace. Scarring is not generally a sequel, although it may result from the primary trauma.

In what specific conditions do we find epithelioid reactions? They are legion and have been lumped together as granulomas. From Table I, one could assume that the new axillary granuloma is most likely a foreign-body reaction.

Although innumerable observations have been made concerning the occurrence of granulomas in clinical states, relatively little has been done experimentally in the study of the epithelioid response. In working with animals, very early investigations showed that dyes, agar, bacteria and bacterial lipids would induce macrophage activity. Recently, Nelson and Lebrun (1956) have found evidence that phagocytosis may involve immune reactions. From their studies with guinea-pig blood, they believe that both antibody and complement are requisite for the *in vitro* phagocytosis of starch granules.

However, the most intensive study of epithelioid response or granuloma formation has centred on the reaction to fatty acids. Sabin, Doan and Forkner (1930) made the original observation that phthioic acid from the tubercle bacillus was capable of calling forth a granulomatous epithelioid reaction in certain animals. Although Harrell (1944) failed to produce any change in human skin with the same material, work has continued in this field. Ungar (1955), in an exhaustive study of many complex synthetic fatty acids, found some which are highly active in producing intra-peritoneal granulomas in guinea-pigs. The three most active are

NN-dimethyl 2 : 4-dimethyl 3 docosylamine HCl

2 : 4 dimethyldocosylamine HCl

2 : 4 dimethyldocosyl-2 enylamine HCl.

TABLE I.

Granulomas in man may result from—

(i) reaction to foreign bodies :

agar	carboxymethyl	magnesium silicate	silica
aluminium hydroxide	cellulose	mercury	starch
aluminium silicate	cotton fibres	metal fragments	sulphonamide
(kaolin)	diatomaceous earth	methyl violet	sutures
barium sulphate	fish bone	mineral oil	talc
beryllium	grain	mucus	thorium dioxide
bone fragments	hair	oils	typhoid vaccine
cactus	keratin	paraffin	urine (sodium urate)
camphorated oil	lipids	polyvinyl alcohol	vegetable matter
chitin	lycopodium	selenium	wood

(ii) the following diseases :

allergic	granuloma annulare	maduromycosis	schistosomiasis
granulomatosis	granuloma inguinale	mycosis fungoides	sporotrichosis
aspiration	granulomatosis	myxoedema	swimming-pool
pneumonia	disciformis	necrobiosis lipoidica	granuloma
blastomycosis	helminthiasis	nephrosis	syphilis
bromoderma	histoplasmosis	pernicious anaemia	tuberculosis
brucellosis	Hodgkin's disease	pyogenic granuloma	tularaemia
coccidioidomycosis	iododerma	regional ileitis	ulcerative colitis
deep fungus	leishmaniasis	reticulohistiocytoma	undulant fever
infections	leprosy	rheumatic fever	Whipple's disease
diabetes	lipophagic granuloma	rhinoscleroma	xanthomatosis
eosinophilic granuloma	lymphogranuloma	sarcoidosis	
	venereum		

The changes noted by Ungar included early necrosis with leucocytic immigration. This was assumed to result from toxic action. At one week, macrophages (monocytes, histiocytes) appeared in the periphery of the lesion and by two weeks, a nodule of epithelioid cells had formed. It is significant that while some of the granulomas resembled those seen in tuberculosis, others were of the foreign-body type. Both Langhans and foreign-body giant cells were seen. A minimum of two to five milligrams of the compounds was required to elicit this response.

Rich (1951) has clearly stressed the significant quantitative aspects of the problem, noting that these fatty acids can hardly be responsible for the formation of clinical granulomas in tuberculosis. No more than one tubercle bacillus is necessary to excite giant-cell formation clinically, whereas these experimental lipids represent many hundreds of milligrams of bacilli.

Another area of great experimental interest (also limited to animal work) has been the production of epithelioid lesions by beryllium and silicon. Fallon and Banting (1935) published excellent illustrations of the effect of injecting quartz (crystalline silica) subcutaneously in rabbits. The best epithelioid response was seen at three weeks. Dutra (1951) made extensive studies on experimental beryllium granuloma formation in pigs. Significantly, he was unable to produce these granulomas in rats or rabbits. Furthermore, in the pig, consistent epithelioid responses were seen only when injections were made into the subcutaneous fat. Injections into the dermis were often without effect. He produced a non-specific inflammatory pattern in the subcutaneous tissue in five days, but in three to six weeks the classic epithelioid granuloma appeared. Metallic beryllium and beryllium oxide were without effect other than producing a scant foreign-body reaction. In contrast, Dutra found that beryllium phosphor with silica (particle size 1.5μ to 3μ) was the only specific excitant of the epithelioid response. Some workers (Helwig, 1951, for example), feel that

all beryllium granulomas are due to the accompanying silica rather than beryllium *per se*.

Shelley and Cahn (1955) described a foam-cell type of granulomatous change in axillary skin. Their studies convinced them that the foam cells were an epithelioid-cell response to extravasated apocrine sweat. They felt that this histological yet clinically inapparent finding resulted in certain individuals in whom apocrine poral closure had developed, leading to apocrine sweat-retention and subsequent rupture of the gland deep in the dermis. It was thus a silent form of apocrine miliaria.

None of these problems has been studied experimentally in man, yet in the study of leprosy and sarcoidosis much has been discovered concerning granuloma formation. As early as 1916, it was found by Mitsuda (1919) that certain leprosy patients formed a local granuloma several weeks after the injection of a suspension of lepromatous tissue. The test material is called "lepromin" and it gives a positive epithelioid response in tuberculoid leprosy but not in lepromatous. It is also possible to elicit this reaction with a suspension or even a crude extract of lepra bacilli. The chemical nature of the test materials is not known, but it is known that purified protein derivative of the bacilli gives only an early non-granulomatous response like the positive tuberculin test (Lowe, 1955). Recently, investigators have shown that such non-specific materials as normal tissue or milk will produce a macrophage-epithelioid response when injected into leprosy patients (Sagher *et al.*, 1953; Kooij and Gerritsen, 1956).

Analogous developments have occurred in the field of sarcoidosis. In 1941, Kveim discovered that the intradermal injection of a suspension of sarcoid tissue would produce a local granuloma in patients who had sarcoidosis. This has been considered by some (James and Thomson, 1955; Nelson and Schwimmer, 1957) as a specific test for the presence of sarcoidosis. Others (Sones *et al.*, 1955) view the Kveim reaction as non-specific, stating that it occurs in certain tuberculous as well as normal subjects. No-one has isolated any chemical from the test material which could be said to be responsible.

It is important to stress that both the Mitsuda and Kveim test must be read weeks after the material is injected. In both, a positive test manifests itself as a small papule appearing in from 1-2 weeks, reaching its maximum size in 4-6 weeks, and then slowly fading away over a period of from 6-24 months. Biopsy is necessary to ascertain the presence of a granuloma for the clinical appearance is simply that of a non-specific papule. Histological readings earlier than 4-6 weeks for either test are commonly non-specific, since the mature epithelioid cell has not yet evolved in its definitive pattern (Rogers and Haserick, 1954).

Aside from the occasional non-specific yet positive Kveim or Mitsuda test, it has not been possible to produce clinical epithelioid granulomas in normal human skin by experimental means. Silicon or beryllium accidentally deposited in the skin produces granulomas after a most puzzling and erratic latent period, so that accurate analysis of the course of events is impossible (Epstein, 1955; Arzt, 1955). We could find few studies of an experimental nature involving

human skin. All of these centred on the failure of a variety of materials to produce granuloma in sarcoidosis patients (Nelson, 1948 ; Danbolt, 1954).

These materials included :

aleuronate	egg-white	phosphatides, soya bean
calcium sulphate	india ink	<i>Pityrosporon ovale</i>
catgut	lymph node	silicates
collodion particles	muscle	talc
dermis, human	paraffin oil	

In contrast, as noted above, intracutaneous normal tissue and milk injections in leprosy cases produced a histiocytic response. The literature did not reveal any experimental studies on the problem of granulomagenesis in normal human skin. One can only conclude that in the absence of disease, the presence of granuloma spells foreign-body reaction to some relatively insoluble particulate matter. (General references : Florey, 1954 ; Halpern, 1957 ; Gans and Steigleder, 1957 ; Chevremont, 1948.)

(ii) The Nature and Composition of Stick Deodorants.

The first appearance of the new axillary granuloma and the introduction of a new type of deodorant, the zirconium stick, both date back to 1955. Since nearly all the patients have a history of having used this new type of deodorant intensive study of a typical example of the zirconium stick deodorant is warranted (Kalish, 1955 ; U.S. Patent Office, 1956).

Basically, the stick is a soap-alcohol gel made up of sodium stearate (soap), ethyl alcohol, carbitol and water. In this is incorporated about 10% of an aqueous 45% solution of sodium zirconium lactate. Small amounts of hexachlorophene and a perfume are added to make the final product. Further consideration must be given to each of the ingredients since each is suspect in the problem of axillary granuloma formation. In the absence of specific information, it can be assumed that the sodium stearate is of the usual high commercial grade, but that as such it contains relatively large amounts of sodium palmitate (possibly up to 50%) and small amounts of sodium oleate, as well as some free fatty-acid impurities. As a candidate for the rôle of the mysterious granulomagenic substance, sodium stearate might seem unlikely, since the daily use of soap by all has never been known to produce a granuloma.

Ethyl alcohol is also an unlikely factor, although denaturants such as brucine sulphate and tertiary butyl alcohol could be present. Carbitol (diethylene glycol mono-ethyl ether) as a congener of glycerine is a compound miscible with water and extensive studies have revealed it to be essentially non-irritating to rabbit skin (Hanzlik *et al.*, 1947). It is, however, absorbed through the skin and if large areas are covered, topical application of carbitol can be fatal to rabbits.

Zirconium deserves close consideration since its introduction in deodorants coincided with the appearance of the granulomas (Blumenthal, 1956 ; Kalish, 1955). Zirconium is a metallic element in group IV, period 5 of the periodic table. It is placed below titanium and above hafnium. Not radioactive, it is a twin of hafnium and as much as 2% hafnium has been found present in the purest zirconium preparations. Zirconium is found in the earth's crust as an oxide or silicate in a concentration of about 0.022%. Sodium zirconium lactate is a recently synthesized water-soluble

Hexachlorophene is a germicidal organic base which has been used for many years in surgical "scrubs." It has never been found to cause any untoward effect even on abraded skin (Best *et al.*, 1951). However, it is water-insoluble and as such could conceivably initiate an epithelioid response. Perfume is the final component under query. It is also an unlikely suspect.

Attention must be directed to special mechanisms which might possibly be causal. The deodorant could produce apocrine sweat-retention with subsequent escape of apocrine sweat, producing an epithelioid response. The possibility has to be considered that some component of the stick in effect produces a Kveim test. In this case, patients with the axillary granulomas should show manifestations of sarcoidosis and this has not been so in clinical studies. The most attractive working theory was that zirconium or another of the components produced a foreign-body granuloma in a manner analogous to that seen clinically after the accidental introduction of beryllium (Dutra, 1949).

Indeed, the possibility that contaminant beryllium or silicon in the stick might be responsible led us to have spectrographic analyses made on the commercial sodium zirconium lactate solution used in our studies. The following reports were received.

Laboratory "D".

Zirconium (as ZrO ₂)	.	.	13.6%
Silicon (as Si)	.	.	0.008%
Aluminium	.	.	Trace
Calcium	.	.	"
Magnesium	.	.	"

Laboratory "C".

Zirconium	.	X.0%	Iron	.	0.00X	Low
Sodium	.	Major	Magnesium	.	0.00XX	"
Aluminium	.	0.00X	Nickel	.	0.00X	
Boron	.	0.00X	Silicon	.	0.00X	
Calcium	.	0.0X	Strontium	.	0.00X	
Chromium	.	0.00X Low				

Elements checked, but not found :

Antimony	Cobalt	Lead	Tin
Arsenic	Columbium	Manganese	Tungsten
Barium	Copper	Molybdenum	Titanium
Beryllium	Gallium	Platinum	Vanadium
Bismuth	Germanium	Silver	Zinc
Cadmium	Gold	Tellurium	

The absence of beryllium and the trace amounts of silicon provide no support for the view that the deodorant granuloma is a beryllium or silicon granuloma.

As a result of the literary survey, it was apparent that experimental study was necessary before any conclusions could be drawn about the nature and cause of the granuloma.

EXPERIMENTAL STUDIES.

(i) Production of Zirconium Deodorant Granuloma under controlled Conditions.

Study of the literature convinced us that granulomas may develop in persons using zirconium stick deodorants. However, it gave us no knowledge of the nature or cause of such a reaction. We could not be certain that the stick itself was responsible for the reaction. Analysis of the problem made it clear that much could be discovered if we were able to produce the granuloma reaction experimentally under known controlled conditions. We undertook



FIG. 3.—Appearance of experimentally-produced zirconium deodorant granuloma.

such an experimental study, limiting our work to man since species differences have at times invalidated the most closely reasoned arguments.

We knew that the granuloma reaction was a clinical rarity which might never develop in the necessarily small group of volunteer subjects we could muster under our personal supervision. Intensive application seemed to be our sole hope. In this effort to raise the incidence rate to a point which would be experimentally rewarding, we had thirty healthy, adult male subjects vigorously rub a standard commercial zirconium stick deodorant in the left axilla every morning for five minutes. The right axilla served as a control for the effect of zirconium, and here a zirconium-free stick deodorant was rubbed daily for the same period. The zirconium and the non-zirconium control stick were identical in composition and appearance,

except that one contained approximately 5% zirconium and the other was completely free of zirconium. Included in the stick base were sodium stearate, ethyl alcohol, water, carbitol, perfume and hexachlorophene. Both axillae were closely shaved every other day. None of the men had used zirconium stick deodorant previously and no deodorants of any kind had been applied for one month before the test period.

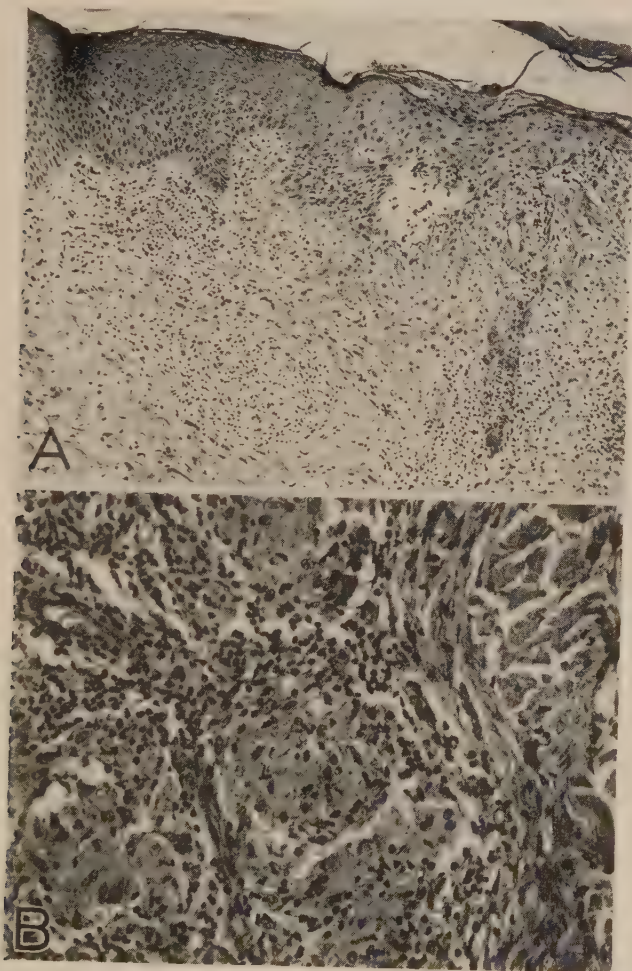


FIG. 4.—Histology of experimentally-produced zirconium granuloma shown in Fig. 3.
(A) Granulomatous nests of pale-staining epithelioid cells in dermis. On the right, a miliarial lesion through which zirconium entered.

(B) High power view of late axillary granuloma of subject No. 2. Nests of epithelioid cells and giant cells in the lower left corner.

No soap, dusting powder or topical applications were used for the entire test period. The test treatment period was ten weeks. Biopsies were taken at appropriate times from both axillae in every subject. These were serially sectioned and stained with haematoxylin and eosin.

After one month, subject No. 2 (white man, aged 33) developed a chronic non-inflammatory eruption of the left axilla (Fig. 3). Two weeks later, some of the papules were excised and histological study revealed an early epithelioid granuloma (Fig. 4,

A and B). Miliaria rubra could be seen microscopically and streaming microparticles were observed entering the dermis through the damaged epidermis. A control biopsy specimen from the clinically normal axilla on the right revealed no histological abnormalities.

After eight weeks, topical applications of the stick were stopped. Subject No. 2's eruption was entirely characteristic of the clinical axillary granulomas following the use of deodorants. Several hundred distinct papules were present. It is important to note that some long linear lesions were seen. These consisted of confluent papules appearing as though the eruption had developed in a razor cut or a long scratch-mark.

A second biopsy secured at 10 weeks showed a fully-formed granuloma of many epithelioid cells, some giant cells and a minimal number of inflammatory round cells. The appearance was that of the naked tubercle seen in sarcoidosis. The eruption was left completely untreated. The course was one of slow involution over a period of months. At five months, a final biopsy was taken of some small residual papules. This revealed many small epithelioid cells. Some inflammatory cells were still present.

We concluded from this study that the intensive topical use of a standard zirconium stick deodorant could lead to the production of granulomas in the normal shaved axilla of a white male. It is a dramatic significant finding that the contra-lateral axilla, receiving exactly the same treatment with a stick identical except for the absence of zirconium, remained completely without change either grossly or microscopically. Thus, repeated topical application of stearate, hexachlorophene, carbitol, alcohol, and perfume produced no granulomas. Zirconium is the critical compound, therefore. In its absence granulomas do not appear.

It is important to record that during the two months' experimental run, three other subjects showed clinical changes in the skin of the left axilla, but in all ten subjects the right axilla remained completely clear except for occasional transitory folliculitis as a result of the trauma of shaving. The following records the pertinent data:

Subject No. 5 (white man, aged 24). Inflammatory papules were seen developing in the left axilla at eight weeks. These closely resembled the clinical appearance of those of the deodorant granuloma. However, a biopsy at ten weeks failed to show the presence of any granulomatous infiltrate. There was epidermitis, with oedema of the corium, vasodilatation, eosinophils and degenerating polymorphonuclear leucocytes. The infiltrate was largely perivascular in location. In addition, spongiosis and vesiculation were seen about the eccrine sweat ducts. The clinical lesions all spontaneously involuted within two weeks of stopping the deodorant. A control biopsy taken from the right axilla was entirely normal. We interpreted the histological changes to indicate that the papules seen in the left axilla were the result of a primary irritant action of zirconium, which led to a dermatitis and miliaria. The zirconium-free stick was by contrast entirely innocuous. The microscopic study stresses the necessity for histological study of all suspected cases of deodorant granuloma. Clinical corroboration of the biopsy findings was provided by the fact that the papules promptly involuted within a few days after stopping the zirconium deodorant.

Subject No. 6 (white man aged 30). This man developed a marked papular eruption of his left axilla six weeks after starting to use the zirconium stick. Biopsy at eight weeks showed an acute inflammatory reaction similar to that seen in subject No. 5.

The eruption disappeared a few days after the zirconium was discontinued. The right axilla was normal both clinically and histologically. This is the second case seen in the experimental studies which mimicked the deodorant granuloma clinically. However, rapid healing and a histological picture of acute inflammation with no epithelioid response eliminated granuloma as the diagnosis.

Subject No. 9 (white man, aged 35). After eight weeks, this subject developed a few small papules in the left axilla. Two weeks later, biopsy revealed a chronic inflammatory response, but no epithelioid change. Control studies on the right side were both clinically and histologically negative.

In summary, intensive prolonged daily application of a commercial zirconium deodorant stick led to the production of a histologically proven chronic axillary granulomatous response in one of thirty male subjects. Three other subjects showed a transitory inflammatory papular response which was non-granulomatous. From these findings it is apparent that zirconium is in some way responsible for the granuloma.

The next step was to investigate the effect of changing the concentration of zirconium and at the same time using a stick from which hexachlorophene, perfume and carbitol had been excluded. The men applied the following preparations for five minutes daily for a period of ten weeks :

Right axilla.	Left axilla.
Sodium zirconium lactate (approx.) 0.5%	Sodium zirconium lactate (approx.) 10%
Sodium stearate	Sodium stearate
Alcohol	Alcohol
Water	Water

The axillae were shaved every other day and all other topical applications were interdicted. Biopsies were taken at appropriate times from both axillae in every subject. These were serially sectioned and stained with haematoxylin and eosin. From the clinical standpoint, folliculitis, primary irritant reactions and miliaria were far more frequent in the left axilla in which the double-strength zirconium was being used. It was in the left axilla, also, in which four subjects developed a papular eruptive change clinically suggestive of a granulomatous response. Biopsies revealed that only one of the four was a granuloma.

Subject No. 35 (negro man, aged 30). After one month in which the axillae were entirely clear, an inflammatory papular eruption appeared in the left axilla. This became plaque-like after six weeks and it did not involute until three months after discontinuing the zirconium stick deodorant. No treatment of any kind was instituted. The right axilla remained entirely clear during the entire ten-week test period. Biopsy of the papules at eight weeks revealed a typical granulomatous infiltrate in the dermis.

Pseudogranulomatous papular eruptions were seen in the following subjects :

Subject No. 36 (white man, aged 30). After two weeks, this subject developed an inflammatory follicular eruption entirely localized to the left axilla. This became papular and persisted for two weeks after the stick applications were discontinued. Biopsy at eight weeks revealed a chronic inflammatory dermal infiltrate, but no granuloma.

Subject No. 41 (white man, aged 35). After six weeks, this subject developed many inflammatory papules on the left side. These proved to be a chronic inflammatory-cell reaction on biopsy at eight weeks. No granuloma was seen. Within one month of stopping the deodorant stick, the eruption had essentially disappeared.

Subject No. 50 (white man, aged 40). After six weeks, this subject developed many inflammatory papules in both axillae. The reaction was so severe as to necessitate discontinuance of the zirconium sticks. Biopsy two weeks later revealed a chronic inflammatory round-cell infiltrate, but no granuloma.

Thus, in these studies, zirconium deodorant granulomas were seen to develop under controlled conditions in two of fifty experimental subjects. These two subjects (Nos. 2 and 35) served as a testing ground for numerous studies which were done over a period of a year to determine the pathogenesis of their unusual response to the topical application of zirconium deodorant sticks. It should be stressed here that this granulomatous reaction pattern was persistent. One year after his initial granuloma, subject No. 2 was re-treated with a 10% zirconium stick. Within two weeks he had developed a histologically proven granuloma. Subject No. 35, re-studied at six months, also showed a granulomatous response to zirconium deodorants applied to the axilla.

It can be concluded that sodium zirconium lactate in a plain sodium stearate soap vehicle can produce a granulomatous response when inuncted into the shaved axillary region of either white or negro men.

(ii) Demonstration of Specific Zirconium Hypersensitivity in experimental Deodorant Granuloma Subjects.

From the above studies it was apparent that a soluble zirconium salt in a soap could initiate a chronic local granuloma in the skin. The specificity of the zirconium was demonstrated by the following experiment.

The two subjects (Nos. 2 and 35), who had been demonstrated to react after zirconium deodorant stick application, had daily applications of an aluminium deodorant stick. After two weeks of application to the shaved axilla, subject No. 2 showed non-specific local irritation, whereas No. 35 had no reaction. Clinical and histologic examination two weeks later showed no evidence of granuloma formation. Thus in two individuals known to react to zirconium deodorant stick, an aluminium stick deodorant produced no granulomatous reaction. This was further evidence that sodium zirconium lactate was responsible in some way for the granulomas.

Patch tests with the zirconium deodorant were uniformly negative in subjects Nos. 2 and 35 and twenty normal control subjects. However, intradermal testing demonstrated that subjects Nos. 2 and 35 showed a unique granulomatous response to the introduction of dilute aqueous solutions of sodium zirconium lactate (Fig. 5, A and B). All areas of skin were reactive. The control subjects showed no response to these test solutions. It was actually possible to titre the sensitivity of subjects Nos. 2 and 35. Using tenfold dilution series, 0.02 ml. was injected superficially into the skin.

Concentrations of intradermal sodium zirconium lactate.				
	1/100.	1/1,000.	1/10,000.	1/100,000.
Controls	0	0	0	0
Subject No. 2 . . .	+	+	0	0
Subject No. 35 . .	+	+	+	0

None of twenty control subjects showed granuloma reactions to zirconium in concentrations as high as 1/100. In contrast, No. 35 produced a granuloma in all intradermal test sites in which the sodium zirconium lactate was present in a concentration of 1/10,000 or higher. Subject No. 2 also produced granulomas if the concentration was 1/1000 or higher.

Neither the experimental subjects No. 2 and No. 35, nor any of the twenty control

subjects showed granulomatous response to the zirconium-free deodorant stick components—stearate, alcohol, carbitol, hexachlorophene, and perfume.

Further study revealed that subjects No. 2 and No. 35 were specifically sensitive to the element zirconium, rather than any particular salt. Injections of zirconium chloride and zirconium nitrate were equally as granulomagenic as injections of sodium

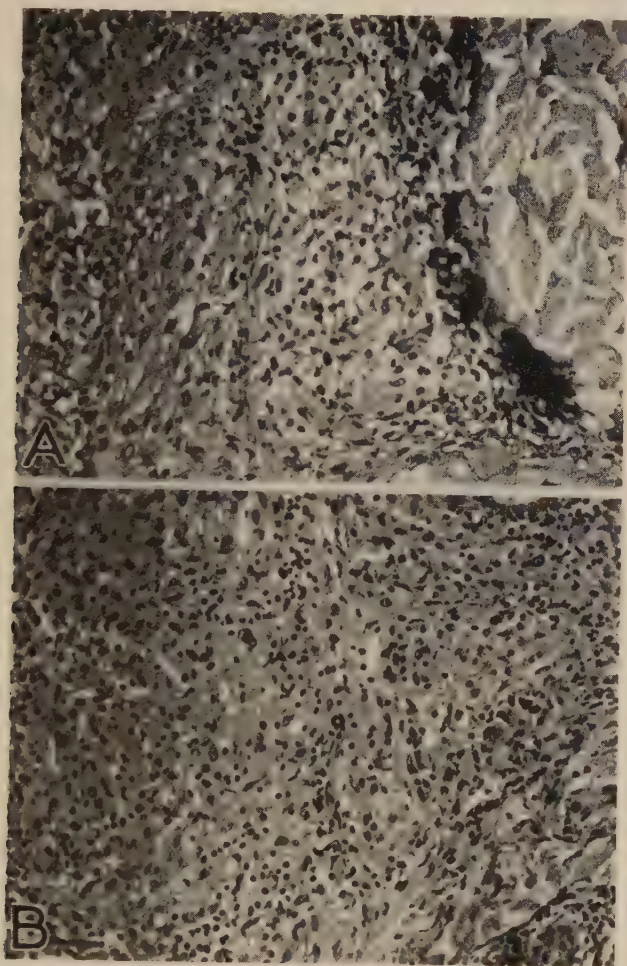


FIG. 5.—Histology of positive allergic granulomatous skin tests following intracutaneous injection of 0.02 c.c. of 10^{-4} sodium zirconium lactate solution.

(A) Experimental subject No. 35. Response at ten days. Note epithelioid cells.

(B) Clinical patient No. 3. Solid granulomatous infiltrate four weeks after the skin test.

zirconium lactate. In contrast, injections of 1/1000 of beryllium sulphate and colloidal silica (Ludox) produced no response in subjects No. 2 and No. 35, or in the control subjects.

It is thus apparent that the two men who developed deodorant granulomas in the experimental studies had a specific hypersensitivity reaction to the zirconium which manifested itself as a granuloma.

(iii) Demonstration of the Allergic Nature of Zirconium Hypersensitivity.

Hypersensitive states may result from either allergic or non-allergic mechanisms. In the present instance we have found evidence which indicates that the hypersensitivity to zirconium which we have observed is allergic in nature.

(a) Allergic states are acquired, not innate or inherited. Although we had no skin tests on subjects No. 2 and No. 35 prior to the development of their zirconium granuloma, it can be presumed that initially they had no hypersensitiveness to zirconium. During the first month or six weeks, this hypersensitivity developed. This was the incubation period for the development of the allergic state. Once the hypersensitivity had developed, further applications resulted in granuloma formation within two weeks. The incubation period was thus replaced by the latent period of a delayed allergic response. More cogent evidence for the fact that zirconium hypersensitivity is acquired is recorded elsewhere (Shelley and Hurley, 1957). In another subject, not part of this study, we observed the acquisition of zirconium hypersensitivity. Initial tests to zirconium were repeatedly negative. Months later, the test sites developed a granulomatous reaction. Further tests with zirconium proved that the subject had become specifically sensitive to zirconium.

(b) Allergic states are specific. Evidence for the specificity of the present zirconium reaction is detailed above.

(c) Allergic reactions are immunological phenomena based upon antigen-antibody reactions. Here zirconium is the antigen. We are in the process of attempting to demonstrate the antibody. Classical serological tests for the union of antigen and antibody have proved unsatisfactory. Zirconium is a metal which precipitates serum proteins from all sera, thus vitiating precipitin or agglutinin test procedures. We have had to rely on modified passive cell and serum transfer procedures. Initial studies with serum have been negative, possibly since, as Lawrence (1956) has pointed out, previously described delayed allergic reactions show no transferable serum antibody. This is in contrast to the immediate-type allergic reaction, although in both, highly specific altered immune responses are known to be operative.

As a result of these studies, it is possible to state that experimental axillary deodorant granuloma is the result of an allergic reaction to zirconium.

CLINICAL STUDIES.

Having demonstrated the nature of the deodorant granuloma in experimental subjects, it was desirable to check the salient findings in a group of patients who had developed the eruption clinically. Each of the following four patients had the typical deodorant granuloma of the axillae. General medical studies were negative and the special studies follow the case reports.

Case 1, white nurse, aged 23. Initial history of developing pruritic, mildly inflammatory rash in both axillae two months after using commercial zirconium deodorant stick. Examination revealed confluent pigmented papules in both axillae. No biopsy was taken and the condition was not identified until a second visit nearly two years later. At that time the patient still had a few very small residual papules. She had used no deodorant for the past two years. On biopsy, the skin showed patchy granulomatous change.

Case 2, white saleswoman, aged 42. On her initial visit she gave a history of having used a commercial zirconium deodorant stick several months prior to the appearance of an eruption in her axillae. On examination four months after the onset of the eruption, she presented numerous pigmented sarcoid-like papules of both axillae. Biopsy revealed a sarcoid-like granuloma. Treatment with topical steroids was without much success. During the course of our observation period of nine months, there was distinct gradual involution of the lesions, but at the time of writing the lesions are still evident thirteen months after the onset.

Case 3*, housewife, aged 33. We saw her 21 months after she first developed a bilateral axillary eruption. This had been papular and was slowly involuting. At that time, she presented a few isolated pigmented papules in both axillae. She gave a history of having used a zirconium deodorant stick for four months prior to the onset of the eruption. Biopsy showed typical granulomatous changes in the dermis.

Case 4, office worker, aged 24. Patient gave a history of having used a zirconium stick deodorant only twice. Immediately thereafter, she developed an eruption which persisted over three months. Examination by us at six weeks revealed a discrete papular eruption of both axillae. Biopsy showed a granulomatous reaction.

The following charts the special studies made on these four patients which indicated that they had an allergic sensitivity to zirconium. The degree of sensitivity varied, being greater in the more severe and chronic cases.

Clinical case no.		Patch test to zirconium deodorant stick (full strength) (72 hours).	Intradermal test (0.02 ml.) sodium zirconium lactate			Intradermal test (0.02 ml.)	
			1/1,000.	1/10,000.	1/100,000.	Beryllium sulphate 10^{-3} .	Silicon dioxide 10^{-3} .
1	.	Negative	+	+	0	0	0
2	.	"	+	+	0	—	—
3	.	"	+	+	0	—	—
4	.	"	+	0	0	—	—

It can be concluded that the experimental and clinical findings are identical. The deodorant granulomas observed in both groups resulted from an allergic reaction to the zirconium ion.

A summary of the features of reported cases of axillary granuloma is given in Table II.

DISCUSSION.

Although certain granulomas have been suspected as allergic in origin (Rich, 1951; Rogers and Haserick, 1954; Bohrod, 1954; Antweiler and Hirsch, 1956; Sterner and Eisenbud, 1951), this is the first direct demonstration in man that the introduction of extremely small amounts of a pure substance may produce a delayed allergic reaction in the form of an epithelioid granuloma.

* Kindly referred to us by Dr. Matthew A. Olivo, of Camden, New Jersey.

TABLE II.—*A Summary of the Reported*

Case.	Sex.	Age.	History.	Clinical (in both axillae in all cases).
1	F.	37	Eruption two weeks after use of zirconium stick deodorant.	Reddish brown papules — some vesicular in appearance. Mild pruritus.
2	F.	30	Used zirconium stick deodorant one month prior.	Flesh coloured, semi-translucent, discrete papules.
3	F.	56	Used zirconium stick deodorant only once 48 hours before pruritic eruption appeared.	At five weeks, shiny brownish-red papules. "Apple jelly" colour on diascopy.
4	F.	31	Chlorhydroxy aluminium sulphate deodorant lotion applied two days prior.	Reddish-brown papules.
5	F.	22	—	1-4 mm. yellowish-pink papules.
6	F.	25	Used cream and lotion deodorants. Had not used stick deodorant.	Several firm linear papules.
7	F.	37	Used zirconium stick deodorant.	Red, shiny-topped papules
8	F.	45	Used zirconium stick deodorant for one year prior.	Initially presented a contact dermatitis which on subsiding left a papular eruption, partly linear.
9	F.	53	Eruption began shortly after using zirconium deodorant stick.	Glistening papules resembling vesicles.
10	M.	52	Eruption appeared after three months of using zirconium stick deodorant.	20-30 small dome-shaped nodules.
11	F.	41	Zirconium stick deodorant used for three months prior to eruption.	Small brownish nodules resembling sarcoid.
12	F.	17	Zirconium stick deodorant used for three months prior to onset.	Pinkish lichenoid papules.
13	F.	28	Zirconium deodorant used for three months prior to eruption.	Pruritic nodules.
14	F.	28	Deodorant used.	Papular.

This is an entirely new facet of immunological response which must be explored in relation to all the granulomatous processes in medicine. Intradermal skin testing must be extended to discover and identify granulomagenic allergens which may be operative in such diseases as leprosy, sarcoidosis, and tuberculosis. On the basis of our work it would appear likely that lepra bacillus extract and sarcoid tissue, used in the Mitsuda and Kveim test respectively,

Cases of Axillary Granuloma.

Biopsy.	Course.	Special tests.	Author.
Tuberculoid granuloma. . Polarograph negative.	Papules gradually involuted in six months.	—	Rubin <i>et al.</i> (1956).
Tuberculoid granuloma. . Polarograph negative.	X-ray therapy and topical steroids without effect. Persisted over 3 months.	—	<i>Ibid.</i>
Granuloma. Polarograph negative. Zirconium to found by spectroscopic exam.	Persisted over ten weeks.	P.P.D. positive in 2nd strength.	<i>Ibid.</i>
Tuberculoid granuloma.	—	—	<i>Ibid.</i>
Granulomatous infiltrate in corium.	Process persisted for over seven months.	—	Pinkus and Botvinick (1957).
None.	Eruption observed for only one week.	—	Foster (1957).
Granuloma.	Persisted for over one year despite ACTH injections, topical steroids.	—	Counter and Winer (1957).
Foreign body granuloma with much phagocytized fat.	Persisted over eight months.	Blood count, urine, cholesterol normal.	Lewe (1957).
Granuloma.	Persisted over three months.	—	Kozikowski (1957).
Granuloma.	X-ray treatment and local measures not effective. Temporary relief with "dry ice" applications.	—	Sheard <i>et al.</i> (1957).
Foreign body granuloma. Photospectrometry negative.	Eruption persisted for over two months. "Dry ice" treatments helpful.	—	<i>Ibid.</i>
Granuloma with many lymphocytes and plasma cells.	Persisted for over four months.	—	<i>Ibid.</i>
None.	Nodules unchanged in four months of observation.	—	<i>Ibid.</i>
Granuloma. Apocrine glands showed distended ducts, rupture of the walls and foam-cell reaction about them.	Persisted for over three months.	—	Saunders (1957).

contain highly specific allergens in trace amounts. Further studies of the tubercle bacillus should also disclose an antigenic substance responsible for the tuberculoid granuloma.

Intradermal skin testing of patients with beryllium and silicate granulomas, as well as tattoo granulomas, should afford a rapid demonstration of specific hypersensitivity to the causative element. In cases of certain other foreign-

TABLE II.—

Further cases reported

Case.	Sex.	Age.	History.	Clinical (in both axillae in all cases).
15-25	.	—	—	—
26-31	.	—	—	—
32-35	.	—	—	—
36-37	.	—	—	—
38-41	.	—	—	—
42-48	.	—	—	—

Further cases shown or reported

49	.	F.	—	Zirconium stick deodorant used for some time prior to onset of eruption.	.	Papular eruption.
50	.	F.	34	Used zirconium stick deodorant for ten months prior to onset of eruption.	.	Scattered, yellowish, follicular papules. Initially there was diffuse weeping, erythema and swelling. Later there was ulceration.
51-62	.	—	—	Eleven of these 12 cases had used zirconium stick deodorant anywhere from two days to one year prior to eruption.	.	Papular, non-pruritic.
63	.	—	—	—	.	Papular.
64	.	F.	22	Stick deodorants were used prior to onset of eruption.	.	Discrete and confluent, round, oval and irregular. "Apple jelly" coloured, flat papules.
65-70	.					<i>See cases reported</i>

body granulomas, the nature of the offending allergen may be ascertained by multiple intracutaneous tests. The allergic state now encompasses part of the granulomatous reactions in the body and appropriate intracutaneous tests must be undertaken in the study of the nature of any granuloma. It should be especially rewarding as a diagnostic procedure in pneumoconioses as well as other examples of occult pulmonary disease.

Increasing experience in this area of allergy will dictate the details of skin

(continued).

but not detailed.

Biopsy.	Course.	Special tests.	Author.
—	—	—	Rubin <i>et al.</i> (1956).
—	—	—	Kahn (1957).
—	—	—	Schiller (1957).
—	—	—	Miller (1957).
—	—	—	Feldman (1957).
—	—	—	Rees quoted by Saunders, 1957b.

at dermatological meetings.

Granuloma.	Masses remained present for over nine months.	—	Jenkins (1956).
Tuberculoid reaction No acid fast bacilli seen.	Slow improvement over a nine-month course. Hydrocortisone topically heals ulcers.	X-ray of chest and small bones normal. P.P.D. second strength positive. Coccidioidin and histoplasmin skin tests negative. Exudate negative for acid-fast bacilli. Serum protein 7.3 g., albumin 5.6 g., globulin 1.7 g., calcium 10.3 mg., alkaline phosphatase 5.3 B.U. Negative Kahn. Blood count normal. Urine normal. Sedimentation rate 9 mm.	Tolman and Moschella (1957).
Tuberculoid granuloma. Spectroscopically negative for zirconium.	Chronic. Oral bismuth preparation appeared to be most effective treatment.	Patch tests to deodorant negative.	Tschan and Wright (1957).
Granuloma.	Chronic.	Patch test was positive with resultant granuloma in site of test.	Higdon (1957).
Sarcoid reaction.	Chronic persistent over a period of sixteen months.	Blood count, urine and chest X-ray normal, tuberculin patch test negative.	Graham (1957).
in this paper.			Shelley and Hurley (1958).

testing procedure. At present, suspect allergens must be given intracutaneously in high dilutions (10^{-4} – 10^{-6}), and in small amount (0.02 ml.). A positive finding can be said to be present if, first, a persistent non-inflammatory papule develops at the test site after a latent period of at least several days. In the case of crude antigens such as a suspension of sarcoid tissue, early non-specific inflammatory reactions may be present, but these will rapidly fade; second, a biopsy at 3 to 6 weeks shows the papule to be composed of granulomatous tissue.

The quantitative aspects of the allergic granuloma deserve special mention since to the clinician they are of a new order of magnitude. Unbelievably small amounts of zirconium may elicit a granuloma. As little as 0.2 μ g. of sodium zirconium lactate was capable of producing a small but grossly visible skin lesion in one of our highly sensitized patients. This introduces, as it were, a new set of micro-dimensions in our thinking on the cause of granulomatous disease. We no longer look for agents such as fatty acids which are needed in milligram quantities to produce granulomas. We now look for agents which act in microgram quantities since they are acting as allergens. The sensitized individual can respond to traces of an allergen well beyond the point which can be detected by present-day physical and chemical analytical procedures. This accounts for the failure of previous workers to demonstrate zirconium in axillary granuloma specimens. Body sensitivity exceeds that of the spectrophotometer.

The present subject of study, the deodorant granuloma, is a prototype of the allergic granuloma. As such, it is significant to sketch its natural history. The affected patients almost uniformly give a history of using a zirconium-containing product for months prior to the sudden appearance of a papular eruption. It is during this period that zirconium sensitivity is arising. During this incubation period, contact with the soap containing 4 to 8% sodium zirconium lactate provides a sensitizing exposure. Shaving is almost universally practised and the nicks permit the soluble salt to enter the dermis in appreciable amount. In a few patients, the initial contact with the zirconium deodorant results in the reaction. In these instances, which are unusual, we can assume that the patient had had prior exposure to zirconium, possibly as an inhalant allergen, with prior sensitization. Once the sensitivity state is present, application of zirconium to the skin results in delayed allergic granuloma formation. Entry may be through shaving cuts and nicks, excoriations, inflammation due to primary irritation, miliaria, contact dermatitis, intertrigo, tape reactions, pyoderma and seborrhoeic dermatitis, or through the pilosebaceous apparatus. Rubbing due to arm movement is a powerful force aiding absorption. Zirconium is an irritant. It retards epithelialization across the shaving cuts and in delicate skin may produce a dermatitis with increased permeability. Miliaria also develops in some people due to poral occlusion caused by the zirconium or simply as a result of maceration due to hyperidrosis. Here permeability is greatly increased at the site of the damaged eccrine pore. We have seen localized granulomas develop just under this site. Although we have not observed it, patients have been seen with an epidermal contact dermatitis resulting from an allergic reaction to one of the components of the stick such as perfume. Here permeability barriers are destroyed. Finally, in patients exquisitely sensitive to zirconium, it is readily conceivable that enough zirconium ion could enter through the normal absorption route of the pilosebaceous

orifice. The entire problem does not loom large in people responding to a few gamma of the element zirconium. It is to be noted that we have observed this granuloma well outside the hairy area in some patients. Here damage to the epidermis had presumably occurred due to chafing, with subsequent increase in permeability.

A critical concentration of zirconium in the stick is necessary, but this must vary from patient to patient. In our experimental studies, when the concentration of sodium zirconium lactate was below 4%, the subject failed to develop a granuloma. This finding can be explained on purely quantitative grounds. In a more sensitive subject, we could expect even trace amounts of zirconium in any deodorant to elicit this response. We have no evidence on the concentration requisite to induce sensitization, but suspect that, in keeping with classical findings in allergy, it must be higher than that required to elicit the response in the already sensitized individual.

Both males and females, both negro and white patients, were observed to develop the disease. Once elicited, the allergic granulomas remained for months. Indeed, traces remained for as long as two years in two of our patients. The general rule appears to be that a high degree of sensitivity is associated with more prominent and longer lasting local reactions. Eventually the eruption can be expected to involute spontaneously without trace.

The deodorant granuloma results from the local introduction of zirconium and lesions therefore have been reported only in the axilla. Nevertheless, the entire skin is sensitized. The lesions do not develop at a distance, but they could appear at any site in which the deodorant had been used. However, the axilla is unique in that frequent rubbing of the apposing surfaces promotes absorption. It is also noteworthy that excessive emotional sweating occurs in the axilla. Thus, miliaria may develop here without regard to seasonal influences.

From the differential diagnostic standpoint, one must consider sarcoidosis (Hall, 1957), Fox-Fordyce disease and localized neurodermatitis. The history, symptoms and histological findings all aid in making a distinction. One further point is of considerable importance. There are many pseudogranulomatous reactions due to zirconium deodorant stick. These mimic the true granulomatous condition but for two important features: they are short lived, disappearing in one to two weeks after the stick is discontinued, and biopsy fails to reveal a granuloma.

Treatment has not been spectacularly effective, but on the basis that this is an allergic reaction, we have used systemic steroid therapy with considerable temporary success. The local injection of sterile hydrocortisone suspension may also induce resolution. This is not a contact dermatitis involving the epidermis, so that pruritus is usually a minor symptom. Topical treatment does not play a major rôle. Obviously, zirconium products must never be

used. The sensitivity persists for years, being present in two of our patients fully two years after the initial reaction.

From the general medical standpoint, these patients are probably best advised to avoid inhalation of zirconium dusts. This could happen in certain occupations in chemical plants and in certain sections of the country. It is conceivable that "zirconiosis" of the lungs could ensue, despite the fact that this entity has never been described in the men mining zirconium. Physicians who deal with individuals working with zirconium must be alert to the possibility of such a new entity.

From the preventive standpoint, zirconium deodorant sticks should not be used by the general public. It must be recognized that this granuloma formation is a very rare development since literally millions of people have used the deodorant without untoward effect. The sensitizing potential of zirconium is clearly very low. Yet the granuloma formation is a very real phenomenon directly attributable to zirconium. At one time at least 30 American deodorant products contained zirconium. It would appear judicious to avoid topical zirconium not only in deodorant sticks, but probably also in the topical treatment of contact dermatitis.

The question arises of the safety of the other non-zirconium containing deodorants. It would appear conceivable that other metals might induce this granuloma response. Yet years of experience with aluminium preparations have failed to reveal such a reaction. It would seem that if aluminium has the capacity to sensitize, it must be extremely low and of no significance to users of deodorants. However, we would not favour the use of aluminium in the stearate stick form until extensive testing had been done. Aluminium salts have not been used in the stearate vehicle and one wonders if stearate could potentiate the sensitizing capacity of a metal, acting as it were, as a Freund adjuvant (Boyd, 1956). It is interesting to note that beryllium was considered as a topical deodorant but preliminary tests showed that it induced allergic contact dermatitis (McCord, 1951). But for this, beryllium might have been employed as a deodorant, only to reveal later its granulomagenic properties.

Our evidence indicates that this heretofore unrecognized allergic response to zirconium is due to the zirconium ion and not to any particular salt or to an impurity. No cross-sensitization phenomena have been encountered as yet, but the possibility of cross-sensitivity to other elements, such as its twin, hafnium, must be borne in mind.

This is an allergic reaction. It is not an ordinary foreign-body granuloma, since here the reaction is to gamma rather than milligrams of zirconium. We found no evidence of apocrine sweat-retention in any of our subjects, nor any histological evidence that apocrine sweat-extravasation is responsible. We feel it is a distinctive new allergic phenomenon to be dissociated from classical

allergic epidermal reactions, as well as the Arthus and Shwartzman responses. It can be identified by skin tests and biopsy.

It is important to comment on the fact that zirconium remains a non-toxic element. It is only the development of the idiosyncratic allergic state which converts zirconium into a harmful pathogenic agent for an individual. Furthermore, the degree of allergic sensitivity acquired must determine the degree of harm which can occur as a result of exposure to zirconium. As in all allergic phenomena the range of this sensitivity is considerable.

Finally, we should like to contrast the non-allergic foreign-body granuloma with the allergic. When appreciable quantities of sodium stearate are introduced into the dermis, a granuloma develops. It was a slow painful process for us to come to realize that the latter was not the duplicate of what we were seeing clinically. Another paper records our work with this non-allergic stearate granuloma (Hurley and Shelley, *in press*) but suffice it to state here that stearate is not responsible for the clinical axillary granuloma since

- (i) large quantities of stearate are required
- (ii) stearate will elicit granulomas regularly in every single individual,
- (iii) stearate granulomas resolve clinically in a few weeks.
- (iv) patients with clinical deodorant granulomas show a normal response to stearate.

SUMMARY.

A review is given of the literature concerning the recently observed axillary eruption associated with deodorants. On the basis of both experimental and clinical studies, it has been shown that these deodorant granulomas result from a specific acquired allergic hypersensitivity to zirconium.

A method of skin testing is outlined which may be employed both for the investigative and diagnostic study of any granulomatous disease.

Attention is directed to the significance of this new vector of allergy in the study of all granulomas in medicine. The finding that trace amounts of a simple metallic ion may produce a granuloma introduces a new aetiological concept in the pathogenesis of disease.

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THE SO-CALLED CUTANEOUS TYPE OF PERIARTERITIS NODOSA.

M. RUITER.

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PERIARTERITIS NODOSA is a form of necrotizing angiitis. This term denotes a type of vascular anomaly which is characterized by fibrinoid changes and inflammatory reactions. Necrotizing angiitides may be generalized and involve internal organs, but they may also, which is less known, be chiefly confined to the skin. The latter group is of particular interest to the dermatologist. In necrotizing angiitides with predominantly cutaneous location we believe that two main groups can be distinguished, apart from the individual characteristics of the vascular lesions: First, a group where the stress of the pathological process falls particularly on the small superficial blood vessels of the dermis; and second, a group which involves the medium-sized muscular arteries, at the cutis-subcutis border or deeper in the fatty tissue.

This classification arose from an attempt to define more closely the clinical dermatological manifestations and to correlate these with the vascular anomalies observed in a number of cases. It refers in particular to necrotizing angiitides which are chiefly or entirely limited to the skin. In the generalized forms with involvement of the internal organs the localization of lesions in the skin is more variable; superficial and deeper reaching cutaneous manifestations often occur side by side.

The clinical dermatological entities corresponding to the vascular lesions of the first group mentioned above (arteriolitis or vasculitis "allergica" cutis) have already been discussed elsewhere (Ruiter, 1952, 1953, 1957). Here we shall chiefly deal with those necrotizing cutaneous vascular anomalies which comprise the second group.

The chief representative of this group is the so-called cutaneous type of periarteritis nodosa. In this disorder arterial branches of the muscular type are mainly affected and the vascular lesions are especially found at the cutaneous subcutaneous border or deeper in the fatty tissue. Clinically, they present deeply situated, somewhat tender nodules and infiltrates about the size of a bean or larger, which may ulcerate (Carol and Prakken, 1937; Miescher, 1946). The lesions are often found on the feet, legs and forearms, but may also occur in other places. It is noteworthy that the histopathology of the vascular alterations in these cases is identical with that described by Kussmaul and Maier in classical periarteritis nodosa. In the cutaneous type, however, the lesions are entirely restricted to the skin.

CASE REPORTS.

Case 1.—A 22-year-old woman (first seen 27 : ix : 55) had been suffering for some time from extensive pyoderma, for which she was given sulphadiazine for a week (5 g. daily) by her family doctor. A few weeks later nodules appeared on the legs, first chiefly on the left lower leg, later also on the right. She complained of fatigue in the calves.

In the following months fresh infiltrates appeared and the older ones subsided spontaneously. Tuberculosis occurred neither in the personal nor in the family history. She did not use any drugs previously.

On examination in September 1955 a number of infiltrated areas could be palpated on both lower legs, the calves and above the ankles (laterally). They were about 1½ cm. in diameter and tender on pressure. The skin covering them was pink to slightly pinkish-blue. In one area the nodules took up a linear arrangement.

General examination.—Normal.

E.S.R.—24. B.P. 130/75.

E.C.G. and chest x-ray : Normal.

Urine—no albumin, no sugar.

Pirquet reaction positive. Serological reactions to streptococci : normal. Culture of a throat swab : no pathogens.

In the beginning of January 1956 the lesions had completely subsided.

Case 2.—A 16-year-old girl had suffered for a year from recurrent, slightly painful nodules on both lower legs. She has not been ill previously and does not take any drugs. The mother had pleurisy at the age of 16. An uncle suffers from pulmonary tuberculosis. The nodules subside slowly but new ones continue to appear.

Clinical examination reveals no internal abnormality. The girl seems to be in fairly good general health. The Pirquet reaction to human tuberculin is positive. E.S.R.—29. Urine—normal.

On the lower legs are 15 to 20 nodules, 2–3 cm. across. The lesions are poorly defined and some are deep-seated. The posterior lower parts of the legs are most affected. Similar elements are also situated at the posterior lateral aspect of the ankles. The skin over these lesions, which are barely elevated, is intact and of a pinkish to bluish-red colour. The nodules are distributed at random : they show no tendency to softening or ulceration and heal without atrophy.

Case 3.—A married woman, aged 30. From 1941 to 1943 she was in a sanatorium with pulmonary tuberculosis and a tuberculous knee. This was followed by convalescence which lasted until 1944. In July 1947 the tuberculous knee-joint was resected. The skin eruption was said to have appeared about 6 months later ; no diagnosis was made on a biopsy performed at this time, and after 5 months it subsided. It recurred 9 months later and biopsy then showed a necrotizing arteritis. On re-examination of the first biopsy necrotizing arterial changes could now also be established.

On examination.—On the lower legs, especially the calves but also on the medial aspect, are a number of pink to pinkish-violet moderately painful indurated nodules and infiltrated areas, 1–2 cm. across. They are barely elevated above the level of the skin. Some lesions, probably older ones, show a more brownish-red discoloration. There is a suggestion of linear arrangement in places. No scars are visible and the elements show no tendency to ulceration.

General examination.—Normal ; urine—normal. E.S.R.—15. The Pirquet reaction is negative with bovine tuberculin, with human tuberculin positive.

HISTOLOGY.

Microscopic examination of the nodules reveals pathological changes chiefly localized in the arterial branches of the muscular type, running along the cutis-subcutis border or deeper in the fatty tissue. In fresh arterial lesions the intima is swollen by fibrinoid necrosis, and the lumen is thus considerably narrowed. Of the swollen endothelial cells in some sections only fragments of nuclei are found. Most striking is the necrosis of the media, which is most pronounced at the transition from media to adventitia (Fig. 1). Here the muscle cells have disintegrated and lie scattered in a fibrinoid necrotic mass together with disintegrated leucocytes. This band-shaped necrosis passes into the adjoining fatty tissue, which shows an inflammatory reaction with much nuclear debris and areas of fibrinoid change. In the same section proliferative changes of the vessel wall can also be seen, with fibroblasts and multinuclear giant cells (Fig. 2). The localized distribution of the vascular changes is revealed by examination of serial sections. As an affected artery is followed the necrotic mass in the media first contains fibroblasts, but within a short distance becomes of normal appearance. The pathological changes in the adventitia extend farther. In older lesions thrombus formation and re-canalization may occasionally be observed. In the vicinity of the affected arteries some degree of fibrinoid change is also found in the walls of small vessels, often confined to the intima. The fatty tissue shows only scattered small inflammatory foci, in Case 2 presenting a tuberculoid structure.

The vascular lesions found in the present cases coincide morphologically with those of periarteritis nodosa of internal organs. The fibrinoid necrosis on the border of media and adventitia of the affected vessels was striking, particularly with medium-sized arterial branches, though sometimes serial sections were needed to demonstrate this. Worth mentioning also is the simultaneous occurrence of exudative with healing vascular processes, attention to which has repeatedly been drawn in connection with periarteritis nodosa.

It seems likely that there is a pathogenetic relationship between the cutaneous type of periarteritis nodosa and arteriolitis (vasculitis) "allergica" cutis. Nevertheless some differences between the two groups can be mentioned, although it is not clear whether these will prove to be of basic significance. Thus in our experience, a personal or family history of allergy is fairly often found in arteriolitis "allergica" cutis and not in the cutaneous type of periarteritis nodosa. Also eosinophils, apparently lacking in most cases of the latter are seldom absent in the former condition. Miescher (personal communication) confirms this observation.

AETIOLOGY AND PATHOGENESIS.

In periarteritis nodosa of internal medicine an allergic genesis is assumed, at any rate in a proportion of cases. This assumption has also much to commend

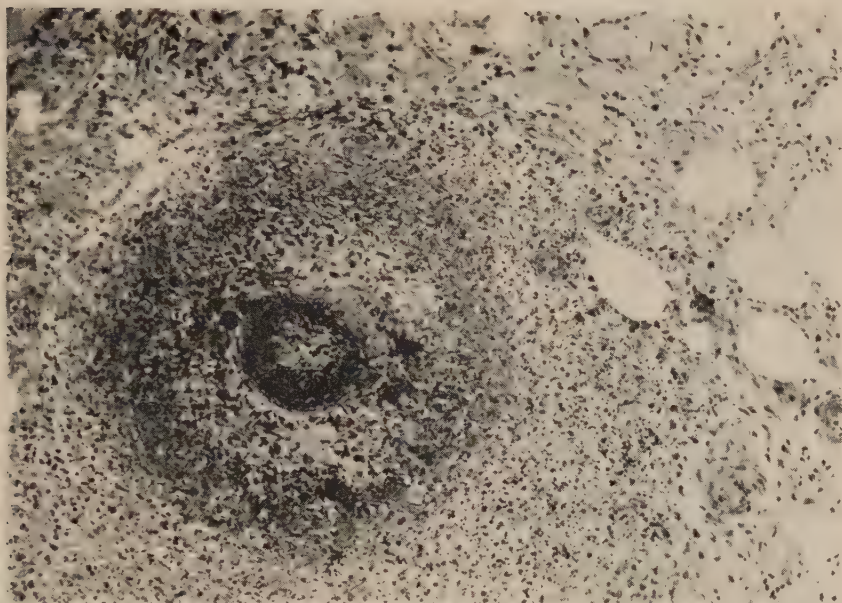


FIG. 1.—Medium-sized artery at the cutaneous-subcutaneous border. Its lumen is occluded by fibrinoid necrosis of the intima and proliferation and swelling of endothelial cells. The media is broadened and necrotic with fibrinoid change. At the transition of media to adventitia is a band-shaped fibrinoid necrosis passing into the surrounding tissues which show severe inflammatory reaction and marked nuclear disintegration. H. & E. $\times 110$.

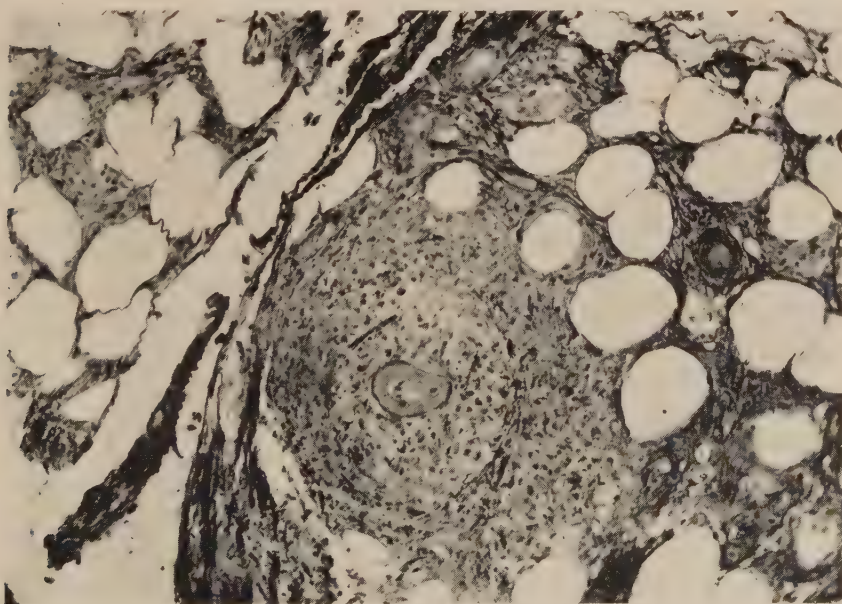


FIG. 2.—Small vessel in the subcutis. The media and adventitia have been replaced by a broad mantle of granulomatous tissue. The intima is swollen by homogenous necrosis. In the same section other arteries showed changes resembling those in Fig. 1. Verhoeff. $\times 110$.

itself for the cutaneous type. In the light of his observations Miescher deemed an infectious-allergic pathogenesis the most likely. It stands to reason that if an allergic pathogenesis can be assumed for periarteritis nodosa then different causal factors can be expected. In Case 1 a sulphonamide hypersensitivity should be considered in the first place. In Case 2 the cause could not be traced with certainty, but there was a tuberculous family history. A possible connection with tuberculosis suggested itself more especially in Case 3, where the cutaneous anomalies were said to have arisen some months after exarticulation of a tuberculous knee joint. It is of interest that Bohrod (1948) reported the occurrence of necrotizing arteritis interpreted as periarteritis nodosa in tuberculous meningitis. It is not clear what connection should be assumed between these vascular findings and the tuberculous infection, but Bohrod believes that such lesions certainly suggest an allergic involvement of the vessel, the allergen being tuberculoprotein.

Our Cases 2 and 3 in particular give occasion to consider the differentiation of the cutaneous type of periarteritis nodosa from erythema induratum. Compared with erythema induratum the distribution of the nodules in our cases of cutaneous periarteritis nodosa was as a rule more arbitrary. Further, they were tender on pressure and sometimes suggested an arrangement in the course of a blood vessel. On the whole they seemed to subside more rapidly than is generally seen in Bazin's disease. Particularly however the histopathology was so highly dissimilar from what is seen in erythema induratum that any suggestion that one is dealing with atypical forms of this disorder is, in our opinion, unacceptable. The arterial changes, which dominated the histological picture, corresponded completely with those of periarteritis nodosa of internal organs. For the nodular cutaneous disorder observed in our patients the denomination "cutaneous type of periarteritis nodosa" seems therefore to be the only fitting one; it is of course possible that a relationship might prove to exist with the classic type, with systemic involvement.

In conclusion, it would be illogical to class this cutaneous type of periarteritis nodosa, which shows a typical histopathological picture, with other nodular cutaneous affections. This seems to be particularly true of "nodular vasculitis", in our view a disorder whose status seems to be rather debatable as yet.

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CALCINOSIS CIRCUMSCRIPTA PRESENTING AS VARICOSE ULCERATION.

STANLEY RIVLIN, M.R.C.S.

Surgeon to the London Varicose Clinic, S.W.11.

CALCINOSIS CIRCUMSCRIPTA is a rare condition, occurring mainly in women of middle or advancing years, who show scattered calcareous radio-opaque concretions in the subcutaneous tissues about the joints of the upper and lower extremities and pelvis. Its aetiology is unknown and may be complex. This appears to be the first recorded instance in which it presented as varicose ulceration.

CASE REPORT.

History.—A woman aged 63 had had varicose veins in the left leg for twenty years. They had been treated by sclerosant injections but had recurred. Thirteen years ago, she became aware of small hard lumps in the pads of three fingers on the left hand. From time to time, small pieces of white chalky material discharged through the skin covering the masses. Seven years ago, she noticed the gradual appearance of a similar but larger mass just beneath the skin of the lateral surface of the middle third of the left leg. Two years ago, she had a severe attack of superficial phlebitis in the left leg, which was treated by rest in bed. Shortly after a small thin white hard piece of material "rather like an egg shell" discharged through the skin, which promptly healed.

During the next twenty-two months, all seemed well except that she saw that her varicose veins were slowly reappearing. (They had temporarily disappeared as a result of the phlebitis). Eight weeks prior to the consultation, a further piece of chalk was discharged. This time, the skin refused to heal and an ulcer soon formed.

Family history.—The patient's mother had had severe varicose veins but there was no other relevant family history.

On examination.—Raynaud's disease was present. The left leg bore gross internal saphenous veins in which the sapheno-femoral valve alone was incompetent. The lower two-thirds of the leg was oedematous and on the lateral aspect there was a reddish area containing three small sinuses (Fig. 1). Beneath each sinus, a hard plaque could be felt and on looking down a sinus, white chalky material could be seen beneath the skin. This was radio-opaque (Fig. 2). The volar surface of three fingers of the left hand contained several small



FIG. 1.



FIG. 2.



FIG. 3.

radio-opaque deposits (Fig. 3) which were of the same consistency as that in the leg.

Treatment.—As the persistent ulceration was due to the presence of oedema consequent upon varicose veins, surgical treatment was advised. Juxta-femoral ligation of the left internal saphenous vein was performed and at the same time a walnut-like piece of calcium (Fig. 4) was removed from the chronic

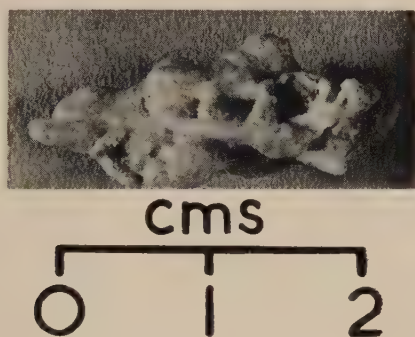


FIG. 4.

ulcer, which was excised. The resulting wound was treated as an ordinary varicose ulcer and allowed to granulate over a period of four weeks, with elastic adhesive ambulatory compression. When seen eighteen months later, apart from a small scar at the site of the former ulceration, the leg was completely normal.

SUMMARY.

Varicose ulceration, though usually occurring after injury, can present in many strange ways. This report describes one of the more unusual—a chronic ulcer at the site of extrusion of a calcium fragment from a subcutaneous plaque in a case of calcinosis circumscripta. Coincidental severe varicose veins and attendant oedema resulted in lack of healing.

I am greatly indebted to Dr. D. M. Smith, the patient's family doctor; also to Dr. Cecil Coyle, and Dr. Michael Ashby of the Whittington Group of Hospitals for access to notes and radiographs.

OBITUARY.

DAVID RHYS LEWIS, M.D., F.R.C.P. (Ed.).

David Rhys Lewis was the second consultant dermatologist to be appointed in Wales and, with his death on 6 July 1957, the Principality lost its senior surviving dermatologist.

Born in 1890, Rhys Lewis was Welsh speaking and devoted to his native land. His medical training began at Edinburgh where he qualified in 1920 and was appointed house physician at the Royal Infirmary. His dermatological studies subsequently took him to Vienna and Paris; he was particularly proud of his brief association with Darier to which he was always delighted to refer.

Before proceeding to his higher qualifications, he served a period in general practice near Swansea and early became engrossed in the occupational diseases which he so frequently encountered in the industrial workers. This interest was to lead in later life to his work on the dermatitis produced by radiant heat in tin workers before it was scheduled under the Workmen's Compensation Act.

In 1931 he was appointed visiting physician at Swansea General Hospital with special care of patients with skin diseases. Soon he was able to devote himself entirely to dermatology and became responsible for dermatological patients over a large area of West Wales. In his later years, he found the travelling of great distances somewhat tedious but this did not affect his unflinching cheerfulness.

His social and professional activities in his home town were multifarious and he had been chairman of the Hospital Medical Staff Committee and of the local division of the British Medical Association. When, in 1950, the name of David Rhys Lewis was picked as High Sheriff of Breconshire considerable pleasure was brought to his family and large circle of friends. He held the office with great dignity and charm, his love of tradition and ritual being allowed full rein. Another honour received by him was his election to the Court of Governors of the National Library of Wales.

The distance of Swansea from London prevented him from being a regular attendant at the Royal Society of Medicine although he sometimes combined a visit with the Dermatological Group Meetings of the British Medical Association. The more accessible meetings of the South West of England and Wales Society of Dermatology he rarely missed, and his breezy manner left no doubt as to his enjoyment of both the social and the clinical aspects of these foregatherings.

Shortly before his untimely death he had relinquished his appointment with the Welsh Regional Hospital Board although the prospect of enforced idleness was irksome to him and he had formulated plans for maintaining his dermatological interests.

Sincere sympathy is extended to Mrs. Rhys Lewis and her daughter, both of whom were regularly seen at dermatological gatherings.

BOOK REVIEWS.

A HANDBOOK OF TREATMENT.*

THE stated objective of this book is a rational, systematic classification of all the topical and internal therapeutic agents which a dermatologist may be expected to know.

It should be realized that this is a pharmacopoeia and not a guide to the treatment of skin diseases, despite its name. There are notes on methods of treatment—for instance, the techniques of using lotions for wet dressings are described at the beginning of the chapter on Liquids—but no attempt is made to specify in any detail when, or for what conditions, wet dressings should be used.

The first part of the book deals with topical applications. It includes the formulae of many of the proprietary preparations which are used in the United States and which are unfamiliar to the British dermatologist, and also all the older traditional prescriptions. Substances are classified according to the physical form in which they are commonly used: thus, sulphur appears in the chapters on Powders, Liquids, Lotions, Creams, Ointments, Soap, Insecticides and Cosmetic Agents.

Many of the references are to formulae alone without any note on the use of the preparation, and some are lists of proprietary preparations which do not state the constituents. This is no criticism of the book, but to the reviewer it was a depressing thought that in this age of active therapeutic agents there should be listed 23 prescriptions for anti-pruritic lotions, all variations on the theme of calamine and zinc oxide.

Although there are warnings about the possibility of sensitivity reactions to such substances as acriflavine and the surface anaesthetic applications, one would wish that the author had been even more dogmatic about the hazards. It is surprising that the topical use of chloramphenicol as a cause of contact dermatitis is not mentioned since it is so commonly seen here.

The second part of the book is a general pharmacopoeia of internal therapy which covers everything from A.B.C. drops to Zyma drops. Although the reviewer strongly believes that dermatology is an integral part of general medicine there seems little of dermatological importance in the pharmacology of digitalis or the urinary antiseptics and diuretics, and much of the information in this part of the book can be found in a text-book of pharmacology.

The final section headed "Reference Data" includes therapeutic measures to counteract poisons, methods of removal of medicinal stains, a table of normal findings of laboratory investigations, a chapter on prescription writing and a useful 30 pages on the dermatological reactions of drugs, hormones, foods and other unclassified agents. The index is accurate and the way in which the information is set out makes for easy reference.

This is a useful book of reference for a dermatological department. It contains much information which cannot be found elsewhere but it is too large and all embracing to be popular as a desk-top reference in the United Kingdom. I. B. S.

* *The Dermatologists' Handbook*. ASHTON L. WELSH. Springfield, Illinois, U.S.A.: Charles C. Thomas. Oxford: Blackwell Scientific Publications. Pp. 427. Price £5 12s. 6d.

SOME IMPORTANT NEW DISEASES.*

"HAVE you any idea what Pamplémousse's Disease is ? No ? Well, let me tell you of a splendid case shown me by my esteemed colleague (a fine fellow, that one) Dr. Braganza."

In his *Maladies-Vedettes*, Dr. Siguier gives accounts of the so-called Collagenoses, temporal arteritis (Horton's disease), necrotising pan-angiitis, periodic disease, Loeffler's syndrome, Sjögren's syndrome (Gougerot-Sjögren), recurrent venous thrombosis, and haemorrhagic states associated with hepatic disease. The text is chatty—almost fireside tittle-tattle—but there is a wealth of information if one can discount the question and answer approach. The reviewer found differential diagnoses well covered, and that of polyarteritis nodosa, for example, particularly thorough. The book is soft covered, and for those who like wielding a paper-knife, many happy evenings may thus be spent. S.C.G.

* *Maladies-Vedettes*. FRED SIGUIER (1957). Paris : Masson et Cie. Pp. 475.

NOTICE.

Proceedings of the Tenth International Congress, 1952.

A few copies of the proceedings are still available, price £3 3s. 0d. They may be obtained on application to : The Editorial Secretary, Xth International Congress, St. John's Hospital for Diseases of the Skin, Lisle Street, Leicester Square, London, W.C.2.

CURRENT LITERATURE.

CHEILITIS ACTINICA AND LABIAL HETEROTOPIA OF SALIVARY GLANDS. R. MICHALOWSKI. (1957) *Dermatologica*, **114**, 373.

Four cases of cheilitis of the lower lip provoked by sunlight had heterotopic mucous glands in the transitional zone of the lip. This probably acts by making the lip more prominent, and so exposing to the sun an area that is normally protected by the upper lip. One of the four patients had the gland-bearing strip excised and has had no recurrence in four years, although much exposed to the sun at his work. The actual mucus secreted on to the lip plays no obvious part in the production of the cheilitis, either through its chemical composition or its refractive index. Only one of the four patients suffered from summer prurigo.

J. F. S.

ULCERO-GUMMATOUS MONILIASIS OF THE GLANS PENIS. M. THAL. (1957) *Dermatologica*, **114**, 368.

This is a description of a gummato-ulcerative condition of the glans penis, from the depths of which candida albicans was isolated. The clinical history, the positive results of tests for pathogenicity of the strain for animals and of serological tests by Janke's method for antibodies to monilia combine to make it highly probable that the organism was the actual cause.

J. F. S.

HYDROLASES IN HUMAN SKIN. F. OTTOLENGHI-LODIGIANI. (1957) *Giorn. ital. Derm.*, **98**, 105.

A review of current knowledge with sections on esterases, carbohydrases, de-aminases and proteases. There are 124 references to European and N. American literature.

A. L.

NECROBIOSIS LIPOIDICA AND ITS RELATIONSHIP TO GRANULOMA ANNULARE. G. PEZZAROSSA. (1957) *Giorn. ital. Derm.*, **98**, 129.

The author believes that necrobiosis lipoidica and granuloma annulare are distinct diseases. His thesis is that necrobiosis lipoidica depends upon a disturbance of the general metabolism of fat in the body, not necessarily due to diabetes mellitus, manifested *inter alia* by a diminished power of holding cholesterol in the serum. Fat is deposited in tissues that have been damaged by deprivation of their blood supply, due primarily to a toxic vasculitis. Granuloma annulare on the other hand depends on local tissue factors and a state of allergic hypersensitivity.

This argument is illustrated by 7 fully documented cases, the first 4 of which are palpably necrobiosis lipoidica and the last 2 granuloma annulare. The fifth case has lesions which look like granuloma annulare but the author assigns it to necrobiosis lipoidica on account of the biochemical, histological and histochemical findings.

Particular reference is made to what is called the "cholesterolytic activity" of the serum. In necrobiosis lipoidica the serum is said to deposit added cholesterol *in vitro*, and in granuloma annulare to dissolve it. The method of assessing this activity is described. The results obtained in the 7 cases are consistent with the author's argument.

A. L.

TREATMENT OF ALOPECIA AREATA BY X-IRRADIATION OF THE SYMPATHETIC. B.UGGERI and A. GIORDANO. (1957) *Giorn. ital. Derm.*, **98**, 177.

Cases that had proved resistant to usual treatments were submitted to irradiation of the whole sympathetic chain. The results were assessed 6 months after starting treatment. Of 12 cases which had been localized to the head 7 had been cured or relieved of disfigurement, 3 were improved but left with bald patches, and 2 were not materially altered. Of 6 cases of total alopecia the corresponding figures were 2, 2, 2. The authors are convinced that this is an effective treatment.

A. L.

CLINICAL OBSERVATIONS ON THE TOPICAL USE OF GLYCYRRHETINIC ACID IN DERMATOLOGY. G. Pozzo. (1957) *Giorn. ital. Derm.*, **98**, 191.

The author treated 50 cases in hospital, 27 of them eczema, with 2% glycyrrhetic acid in a soft paraffin base, and also with this same ointment to which had been added 0.1% bacitracin and 0.05% neomycin. His clinical impression was that both ointments controlled the eczema reaction provided that they were applied at least 3 times a day.

A. L.

GLUCOSE METABOLISM IN PSORIASIS. A. RIBUFFO. (1957) *Giorn. ital. Derm.*, **98**, 3.

An exhaustive consideration of skin biochemistry with a comprehensive review of the recent literature and a report on the effect of injecting glucose and fructose intravenously. There is an excess of sugar in the skin of the psoriatic, both in affected and unaffected areas. The abnormality in psoriasis is differentiated from that in diabetes mellitus.

A. L.

THE INTERPRETATION OF CEMENT DERMATITIS. A. FABIANI. (1957) *Giorn. ital. Derm.*, **98**, 23.

Observations on workmen employed on a hydro-electric scheme showed that dry cement was handled with impunity, wet cement produced hyperkeratosis and fissuring of the hands, and finely emulsified cement a severe, acute dermatitis. While not denying the diagnostic value of a positive patch test to chrome the author believes that cement damages the skin by virtue of its alkalinity.

A. L.

THE SCAR IN PLASTIC SURGERY. D. ROSSELLI. (1957) *Giorn. ital. Derm.*, **98**, 31.

A plastic surgeon's practical classification of scars and his relative and absolute indications and contra-indications to operation.

A. L.

THE REACTION OF INCOMPATIBILITY AGAINST SKIN HOMOGRAFTS : MORPHOLOGICAL ASPECTS AND BIOLOGICAL SIGNIFICANCE. G. RADICI and A. PIREDDA. (1957) *Giorn. ital. Derm.*, **98**, 49.

Using rabbits the authors compare the reactions to homografts and autografts of skin by studying the cytology of the regional lymphatic glands. The plasma cell response provoked by homografts is explained as an immunity reaction.

A. L.

THE FIRST CASE OF INDIGENOUS CUTANEOUS LEISHMANIASIS IN THE PROVINCE OF PARMA. G. PEZZAROSSA. (1957) *Giorn. ital. Derm.*, **98**, 65.

A classical case, treated with chloroquine. The path of infection is speculative.

A. L.

THE HISTOGENESIS OF BROOKE'S EPITHELIOMA AND JACQUET AND DARIER'S HIDRADENOMA AND THEIR RELATIONSHIP WITH BASALIOMA. G. BUCELLATO. (1957) *Giorn. ital. Derm.*, **98**, 229.

A woman aged 25 had noticed a pinkish-yellow papular eruption of the trunk at the age of 11, and it had developed fully by the age of 15. She also had numerous soft, warty naevi on the trunk, a large plane pigmented naevus, and symmetrical colourless naevi. The pinkish-yellow papular eruption was diagnosed as hidradenomas eruptifs (Jacquet and Darier) and two of the lesions were excised and sectioned. The histology showed an apparent hidradenoma, and also proliferation of strands and cords of epithelium reminiscent of Brooke's tumour. Serial sections demonstrated a connection between the "hidradenomatous" tissue and immature hair follicles, and the author concludes that sweat glands had nothing to do with the origin of the "hidradenoma". He classifies both diseases among the basal cell tumours of benign course.

A. L.

OBSERVATIONS ON THE PROTEIN FRACTIONS OF BLISTER FLUID. M. BONELLI and L. DATOVO. (1957) *Giorn. ital. Derm.*, **98**, 253.

The authors are interested in the relationship between the serum proteins and the protein content of blister fluid. They studied blisters in 4 cases of pemphigus, 9 cases of dermatitis herpetiformis, 1 case of herpes gestationis and 5 subjects on whom blisters were provoked with cantharides. In general the proteins in the blister fluid were a three-quarter strength replica of the serum proteins, but there were some minor differences in the various fractions. The serum protein values in all the diseases were abnormal.

A. L.

OBSERVATIONS ON SOME CASES OF "ECZEMATID-LIKE PURPURA". E. CSERMELY. (1957) *Giorn. ital. Derm.*, **98**, 265.

The seven middle-aged patients developed an erythematous eruption which started on the ankles, spread slowly over the body, and faded to brown. Some purpuric lesions were found, but blood investigations were always and capillary fragility tests usually negative. There was an inflammation in and around the superficial capillaries, and the overlying epidermis was mildly oedematous, which accounted for the insignificant scaling observed clinically. The name is

derived from an article by C. Doucas and J. Kapetanakis (1953) *Dermatologica*, 106, 86. There are apparently certain differences between the two sets of cases. The cause of the eruption is assumed to be a circulating toxin, but neither drugs nor substances absorbed from the clothing have been considered in this connection. A. L.

REMARKS AND OBSERVATIONS ON A CASE OF XANTHOMA TUBEROSUM. G. PEZZAROSSA. (1957) *Giorn. ital. Derm.*, 98, 279.

A sporadic example in a man who had gall-stones. His liver was palpable and tests showed some dysfunction. The high blood fat (cholesterol 720 mg. %) subsided to almost normal (cholesterol 260 mg. %) and the skin lesions disappeared during a period of 2½-months' treatment with a low fat diet and an oral preparation of hogs' gastric mucosa. The author believes that the skin disease is an outward and visible sign of an abnormal fat metabolism and demonstrates negative cholesterolytic activity of the serum—see his article on necrobiosis on page 129 of this volume. A. L.

KERATINIZATION OF THE DUCT OF THE SEBACEOUS GLAND AND GROWTH CYCLE OF THE HAIR FOLLICLE IN THE HISTOGENESIS OF ACNE IN HUMAN SKIN. EUGENE J. VAN SCOTT, and ROSS C. MACCARDLE. (1956) *J. invest. Derm.*, 27, 405.

Twenty biopsies from the upper part of the back, 13 with acne and 7 without; 2 from beard region affected by acne, one control; all but one of the biopsies of scalp from patients with alopecia areata, one with early calvities.

Serial horizontal sections; balsa-wood reconstructions of follicle and of contents of follicle.

Of 46 hair roots in lesions studied 39 or 85% were in the resting (telogen) phase as compared with nearly even numbers in the uninvolved follicles of acne patients. Does the secretion of the sebaceous gland change during katagen so that it provokes hyperkeratosis in the parts of the follicle with which it comes into contact? Does steroid bring about acne by prolonging telogen?

The arguments for and against such speculations and many others besides are here, together with anatomical information about the pilosebaceous follicle, all most elegantly presented.

J. H. T. D.

URINARY EXCRETION OF CREATINE AND CREATININE IN DERMATOMYOSITIS. HERBERT B. CHRISTIANSON, PAUL A. O'LEARY, and MARSCHELLE H. POWER. (1956) *J. invest. Derm.*, 27, 431.

The excretion of creatine and creatinine was studied in 134 patients with dermatomyositis and 27 patients with other diseases. That of creatinine is reduced in dermatomyositis as it is in other diseases with muscular degeneration. The normal production of creatine by the liver exceeds the rate of its consumption by the damaged muscles in dermatomyositis but there are other conditions in which the output of creatine may be raised and appear in large quantities in the urine. Determination of urinary creatine and creatinine is of little value in the diagnosis and prognosis of dermatomyositis. J. H. T. D.

ETHER SOLUBLE SUBSTANCES ON THE SKIN OF THE HUMAN EXTERNAL AUDITORY CANAL. S. P. CHIANG, C. F. GESSERT, O. H. LOWRY, and B. H. SENTURIA. (1956) *J. invest. Derm.*, 27, 443.

They have clearly taken a lot of trouble to get this right and their methods deserve study. But it is doubtful if the 16 healthy adults on whom the estimations were made is a number big enough to be representative of the very wide range of differences seen in meatus that have been the subject of no particular complaint. J. H. T. D.

EVALUATION OF FACTORS WHICH MAY BE OF IMPORTANCE IN THE PRODUCTION OF EXTERNAL EAR INFECTIONS. B. H. SENTURIA and F. M. LIEBMANN. (1956) *J. invest. Derm.*, 27, 291.

An experiment, employing the ears of 76 cats, designed to demonstrate the effects in the external meatus of trauma, removal of lipoids, variation of humidity and temperature, and infection; presumably in the hope of extending the knowledge to maladies of the human auditory meatus.

(It seems that while otologists no longer promiscuously diagnose mycosis they have not yet understood the possibility of endogenous affections of the skin.) J. H. T. D.

CUTANEOUS NERVES IN RELATION TO EPITHELIAL TUMOURS. R. K. WINKELMANN.
(1956) *J. invest. Derm.*, 27, 273.

Nerve fibres merely survive involvement in the spread of malignant neoplasms; there is no evidence for innervation. J. H. T. D.

OBSERVATIONS ON RURAL AND URBAN RINGWORM. L. K. GEORG, E. A. HAND and R. A. MENGES. (1956) *J. invest. Derm.*, 27, 335.

The account of 173 cases seen by one of the authors in his private practice during 5 years. All specimens of material of animal origin were carefully selected by the patients and the mycology was studied. J. H. T. D.

OBSERVATIONS ON UREA-EXTRACTABLE SUBSTANCE OF THE HUMAN ABDOMINAL EPIDERMIS. A. G. MATOLTSY and F. S. M. HERBST. (1956) *J. invest. Derm.*, 27, 263.

There is no constituent of epidermis specifically extractable by urea—6 M urea is no more and no less efficient a solvent of protein than, for example, neutral phosphate buffer with or without sodium chloride. The only difference is that, according to the evidence of electrophoresis, it may very well be altering the structure of the protein molecule in the process. J. H. T. D.

MICROCHEMICAL STUDIES ON NORMAL CERUMEN. II. THE PERCENTAGE OF LIPID AND PROTEIN IN CASUAL AND FRESH CERUMEN. S. P. CHIANG, O. H. LOWRY and B. H. SENTURIA. (1957) *J. invest. Derm.*, 28, 63.

The only factor influencing the composition of sebum of which, as the result of these studies, the authors can be at all sure is the interval elapsing since the meatus was last cleaned out by their standard method. J. H. T. D.

IDIOPATHIC HYPERLIPAEMIA AND PRIMARY HYPERCHOLESTEREMIC XANTHOMATOSIS. VIII. EFFECTS OF PROTAMINE ON THE ELECTROPHORETIC AND ULTRACENTRIFUGAL CHANGES PRODUCED IN THE SERUM BY HEPARIN. W. F. LEVER and M. E. LYONS. (1956) *J. invest. Derm.*, 27, 325.

"Four patients with idiopathic hyperlipaemia and 3 patients with primary hypercholesteremic xanthomatosis were given first an injection of heparin and then one of protamine.

"In idiopathic hyperlipaemia heparin produced, in the electrophoretic pattern, an increase in the speed of migration of the lipoproteins resulting in the development of a pre-albumin component representing the α lipoproteins. The subsequent administration of protamine caused disappearance of the pre-albumin component. In the ultracentrifugal pattern, heparin caused a shift of lipoproteins from the higher to the lower S_f classes. This shift was reversed by protamine.

"In primary hypercholesteremic xanthomatosis heparin caused an increase in the speed of migration of the β lipoproteins so that they migrated with the speed of α -2 globulin. This acceleration in the speed of migration was abolished by protamine. Because the serum of our patients with primary hypercholesteremic xanthomatosis contained no lipoproteins of high S_f classes, heparin produced no changes in the ultracentrifugal pattern. Protamine produced no changes either.

"It is not possible to decide from our observations whether protamine acted by neutralizing heparin or by acting independently of heparin." J. H. T. D.

CONTAMINANT FILTERABLE AGENT DERIVED FROM A HUMAN WART. BENJAMIN V. SIEGEL. (1956) *J. invest. Derm.*, 27, 379.

This study of the virus that Bivins (1953, *J. invest. Derm.*, 20, 471) grew on CAM from his own wart shows it to have been a contaminant, probably canary pox. Neutralization tests distinguished it from fowl pox; intracerebral day-old mice inoculation and agglutination tests excluded vaccinia; intracerebral 4-week mice and neutralization tests with rabbit antiserum excluded *H. simplex*; and analogous tests were employed to exclude ectromelia and myxomatosis.

Finally the virus did produce authentic poeks in canaries and it failed to provoke warts in the skin of 4 young men. J. H. T. D.

FACTORS AFFECTING THE DIFFUSION OF DRUGS FROM VEHICLES TO THE SKIN SURFACE. J. B. SHELMIRE, Jr. (1956) *J. invest. Derm.*, 27, 383.

Intensity of coloration of the skin surface by dyes incorporated in the vehicle to be tested is the criterion used in these thoughtful and attractively presented studies. J. H. T. D.